REMARKS

Status of claims

Claims 1, 3-6, 8, 10-13, 32-34 and 37-42 are pending.

Claims 1, 3-6, 8, 10-13, 32-34 and 37-42 have been rejected.

By way of this amendment, claims 11 and 32 are canceled and claims 1, 12, 13 and 33 are amended.

Upon entry of this amendment, claims 1, 3-6, 8, 10, 12, 13, 33, 34 and 37-42 will be pending.

As the Official Action indicates, applicants' previous response stated that claim 32 was canceled but continued to list it as a pending claim. Applicants intended to cancel claim 32 and inadvertantly included it in the list of pending claims. By way of this amendment, claim 32 is hereby canceled properly.

Summary of the Amendment

Claim 11 has been canceled. Subject matter contained in claim 11 is now incorporated into claim 1 as amended.

Claim 32 has been canceled to clarify Applicants' earlier intention to cancel the claim.

Claims 1, 12 and 13 have been amended to incorporate specific references to the types of non-cellular particles used in the claimed methods. Support for the amendment is found throughout the specification and originally filed claims. No new matter is added.

Claim 33 has been amended to specify that the ligand is a fusion protein that comprises a CD28 or a portion thereof and a particular viral portion. Support for the amendment is found throughout the specification and originally filed claims. No new matter is added.

Claim Rejections under 35 USC 112, first paragraph

Claims 1, 3-6, 8, 10-13, 32-34 and 37-42 stand rejected under 35 U.S.C. 112, first paragraph, for the reasons of record (Paper 14) that are also addressed in the current Official Action, i.e. as containing subject matter which is alleged to as not being

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully disagree.

Claims 11 and 32 have been canceled and the rejection as applied to them is moot.

It is asserted that the teachings in *Guibinga et al.* raise doubt of the predictability of the operability of claimed invention because the claims encompass the use of CD28 as part of an adenoviral vector. Since *Guibinga et al.* teach that the activation of the CD28 signal pathway leads to immune responses against the adenoviral vector and since the claims encompass the use of CD28 with an adenoviral vector, there is doubt that the claimed invention would be predictable to those skilled in the art. The claims have been amended to recite that the particles are liposomes or cationic amphiphile-nucleic acid molecule complexes. Accordingly the claimed invention no longer encompasses adenovirus particles. The teachings that prevention of activation of the CD28 pathway inhibits an anti-adenovirus immune response that would otherwise occur if the CD28 pathway was activated no longer raise any doubt as to the predictability of the invention. The claimed invention is not directed at adenovirus vectors and expressly refers to liposomes and cationic amphiphile-nucleic acid complexes. Nothing in *Guibinga et al.* provides any reason to doubt that liposomes and cationic amphiphile-nucleic acid complexes which include a CD28 protein or fragment thereof that interacts with CD80/CD86 would not be expected to work. There is nothing in *Guibinga et al.* suggesting that an immune response analogous to the anti-adenovirus response associated with activation of the CD28 pathway reported in *Guibinga et al.* would be induced against an liposome or cationic amphiphile-nucleic acid complex. It is also asserted that the teachings in *Guibinga et al.* indicate that a non-specific immune response induced by activation of the CD28 signaling pathway would also render the expectation of success in practicing the invention unpredictable. *Guibinga et al.* does not discuss inoperability of an liposome or cationic amphiphile-nucleic acid complex due to CD28 signal pathway activation. Moreover, two references cited in the prior art rejection of the claims suggest using CD28 to target retroviral infection. One skilled in the art reviewing all of the art of record would have no reason to doubt the predictability of success in practicing the claimed invention beyond those embodiments which include adenovirus vectors. The

claims have been amended such that adenovirus vectors are not encompassed by the claims. Accordingly, the teachings in *Guibinga et al* do not raise doubt of the predictability of the claimed invention sufficient to support a rejection under the first paragraph of section 112.

The Office has rejected Applicants assertion that *Deonarian* does not support the rejection but rather supports Applicants' assertion. As stated in the previous response, *Deonarian* refers to the inefficiency of receptor mediated, targeted gene delivery and reports that it is inefficient. It has been asserted that the inefficiency reported by *Deonarian* supports the conclusion that the invention is not enabled because the receptor mediated, targeted gene delivery reported by *Deonarian* works at a less than optimal level and receptor mediated, targeted gene delivery of genes encoding therapeutic proteins encompassed by the claims would be unlikely to be effective if the delivery worked at a less than optimal level. There is nothing in *Deonarian* or any other evidence of record to support the Office's assertion that suboptimal gene delivery indicates a reason to doubt the predictability of the invention. The conclusion provided is unsupported by any reasoning or evidence. Applicants' assert that the invention is enabled and *Deonarian* supports this assertion.

The Official action indicates that Applicants' assertion that none of *McCluskie et al., Torres et al* and *Nakano et al.* support the rejection is not persuasive. The rejection indicates that the claimed invention is not enabled because the specification is silent with respect to administration regimens and that such disclosure is necessary to support the breadth of the claims. Applicants respectfully urge that the reasoning provided to support the rejection is contradicted by the evidence offered to support the reasoning. The Official action refers to the teachings of *Nakano et al,* raise doubts of the enablement of the invention. *Nakano et al.* indicate that different routes of administration have a quantitative and qualitative effect on the immune response generated against an immunogenic protein encoded by plasmid DNA delivered to cells. Applicants respectfully urge that *Nakano et al* support a finding of enablement rather than raise doubts. Specifically, *Nakano et al* does not teach that it is unpredictable whether or not delivery of DNA encoding an immunogenic protein will lead to induction of an immune response or not. of enablement rather than raise doubts. Specifically, *Nakano et al.* teach

that an immune response is predictable although it will vary depending upon where the DNA is administered. Nothing in *Nakano et al.* raises doubts as to whether or not one of ordinary skill in the art would expect the invention to work. Rather, *Nakano et al.* provides those skilled in the art with an expectation that the invention will work.

The evidence of record supports the conclusion that the claims are enabled. The evidence of record supports the conclusion that one having ordinary skill in the art would not doubt Applicants' assertion that the claimed invention is enabled. Weighing the totality of the evidence of record, one skilled in the art would have a reasonable expectation of success. The burden of establishing that the claims are not enabled requires the Office to put forth sufficient reasoning and evidence sufficient to support a conclusion that one skilled in the art would doubt Applicants' assertion that the invention is enabled. Not only has the burden not been met but the evidence of record would lead one of skilled in the art to have a reasonable expectation of success.

The claims are enabled. Applicants respectfully request that the rejection under 35 USC 112, first paragraph be withdrawn.

Claim Rejections under 35 USC 112, second paragraph

Claims 1, 10, 33, 34 and 37-42 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is asserted that the each of these claims are indefinite because the phrase :the viral portion" in claim 33 lacks an antecedent basis.

Applicants respectfully note that any lack of antecedent basis in claim 33 should not effected the clarity of claims 1 and 10. Applicants have amended to claim 33 to more clearly define the invention. As amended, claim 33 provides antecedent basis for all terms used. Applicants respectfully submit that the amendment of claim 33 obviates this rejection.

As amended, the claims are clear and definite and in compliance with the requirements of the second paragraph of 35 USC 112. Withdrawal of the rejection is respectfully requested.

Claim Rejection under 35 USC 102

Claims 1, 10, 11, and 13 have been rejected under 35 U.S.C. 102(e) as being anticipated by *Wong-Staal et al* (US 2001/0007659).

Wong-Staal et al teach a method of introducing a nucleic acid into a dendritic cell that expresses CD80 and/or CD86 using a lentivirus vector. *Wong-Staal et al* disclose on page 4, paragraph 0031 incorporating a binding domain for CD86 including CD28 (containing the extracellular region) in the coat protein of the lentiviral vector retrovirus particle.

Claim 11 has been canceled and the rejection with respect to it is moot.

Claims 1 and 12 have been amended to specifically recite that the particle is a liposome; or a cationic amphiphile/DNA complex. *Wong-Staal et al* neither teaches nor suggests using non-viral particles as a delivery vehicle but rather is solely and specifically directed to the use of lentivirus vectors. *Wong-Staal et al* teach attaching a CD80/CD86-binding fragment of CD28 to a structural protein of the viral particle. Each of claim 1, 10 and 13 include limitations not found in the *Wong-Staal et al* reference. Accordingly, claims 1, 10 and 13 are not anticipated by *Wong-Staal et al.*

Applicants respectfully request that the rejection of claims 1, 10 and 13 under 35 U.S.C. 102(e) for being anticipated by *Wong-Staal et al* be withdrawn.

Claim Rejections under 35 USC 103

Wong-Staal et al* in view of *Paul et al

Claims 1, 8., 12, 32-34, 41, and 42 have been rejected under 35 U.S.C. 103(a) as being unpatentable over *Wong-Staal et al*, in view of *Paul et al* (US 5,736,387).

Wong-Staal et al teach a method of introducing a nucleic acid into a dendritic cell that expresses CD80 and/or CD86 using a lentivirus vector. *Wong-Staal et al* disclose on page 4, paragraph 0031 incorporating a binding domain for CD86 including CD28 (containing the extracellular region) in the coat protein of the lentiviral vector retrovirus particle.

Paul et al teach the use of a chimeric (fusion) targeting ligand in a retroviral vector in order to direct gene delivery to a specific mammalian cells. The ligand incorporated into the viral particle of the retroviral vector comprises a ligand moiety

capable of binding to receptors present on target cells, and an uptake moiety capable of promoting entry of the vector into the target cell. *Paul et al* disclose that the chimeric targeting ligand can comprise HIV gp41 protein including the cytoplasmic and transmembrane regions. *Paul et al* do not specifically teach or suggest a chimeric targeting ligand that can comprise CD28 or a portion thereof.

It is asserted that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Wong-Staal et al* and *Paul et al*, by simply selecting CD28 as the ligand moiety for dendritic cell targeting with a reasonable expectation of success. It is asserted that the ordinary skilled artisan would have been motivated to modify the claimed invention because the gp41 uptake moiety in the chimeric targeting protein produces additional means for delivering nucleic acids into the cells. It is thus asserted that the claimed invention as a whole was *prima facie*. Applicants respectfully disagree.

Claims 1 and 12 have been amended to specifically recite that the particle is a liposome; or a cationic amphiphile/DNA complex. Claim 32 has been canceled and the rejection as applied to claim 32 is moot. Claims 8, 33, 34, 41 and 42 indirectly dependent on claim 1 and therefore contain all of the limitations of claim 1. Neither *Wong-Staal et al* nor *Paul et al*, teaches or suggests using non-viral particles as a delivery vehicle. Rather each reference is solely and specifically directed to the use of retroviral vectors. Both references tech making a fusion protein with a structural protein of a viral particle that is then incorporated into the viral particle upon assembly. Nothing in either reference would motivate one skilled in the art to proceed with any delivery vehicle other than retroviral particles. Both references are specifically directed at improved viral vectors and the teachings with the references do not suggest use of any other type delivery vehicle. *Paul et al* specifically indicates that the gp41 portion of the fusion protein is provided to facilitate viral uptake. Nothing in either reference suggests using gp41 in a non-viral delivery system.

Claims 1, 8, 12, 33, 34, 41 and 42 are not obvious in view of the combination of *Wong-Staal et al*, and *Paul et al*. Applicants respectfully request that the rejection of claims 1, 8, 12, 33 and 34 under 35 U.S.C. 103(a) as being unpatentable over *Wong-Staal et al* (US 2001/0007659), in view of *Paul et al* (US 5,736,387) be withdrawn.

Wong-Staal et al* and *Paul et al* in view of *Sedlacek et al.

Claims 3-6, and 37-40 have been rejected under 35 U.S.C. 103(a) as being unpatentable over *Wong-Staal et al* and *Paul et al* as applied to claims 1, 8, 12, 32-34, 41, and 42 above, and further in view of *Sedlacek et al* (US 6,358,524).

Wong-Staal et al teach a method of introducing a nucleic acid into a dendritic cell that expresses CD80 and/or CD86 using a lentivirus vector. *Wong-Staal et al* disclose on page 4, paragraph 0031 incorporating a binding domain for CD86 including CD28 (containing the extracellular region) in the coat protein of the lentiviral vector retrovirus particle.

Paul et al teach the use of a chimeric (fusion) targeting ligand in a retroviral vector in order to direct gene delivery to a specific mammalian cells. The ligand incorporated into the viral particle of the retroviral vector comprises a ligand moiety capable of binding to receptors present on target cells, and an uptake moiety capable of promoting entry of the vector into the target cell. *Paul et al* disclose that the chimeric targeting ligand can comprise HIV gp41 protein including the cytoplasmic and transmembrane regions. *Paul et al* do not specifically teach or suggest a chimeric targeting ligand that can comprise CD28 or a portion thereof.

Sedlacek et al teach a method for inserting genes into a number of specific cell types comprising delivering a complex into cells of an organism. The complex comprises a non-viral carrier such as cationic amphiphile/DNA complex ; a ligand that binds specifically to a receptor that is found on the desired target cell; a fusogenic protein, such as HIV gp41, for the penetration of the vector into the cytoplasm of the target cell; and a nucleic acid molecule to be introduced into the cell. The nucleic acid molecule, is preferably a plasmid, includes the gene's coding sequence and is provided with regulatory regions. *Sedlacek et al* do not teach or suggest using CD28 as a ligand for targeting cells that express CD80/CD86.

As noted in the Official Action, the combined teachings of *Wong-Staal et al* and *Paul et al* do not teach delivering a DNA molecule. It is asserted nonetheless that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Wong-Staal et al, Paul et al, and Sedlacek et al* by simply selecting CD28 as the ligand moiety for delivering a DNA molecule to

dendritic cells and fusing the ligand with the fusogenic gp41 with a reasonable expectation of success. It is asserted that the ordinary skilled artisan would have been motivated to modify the claimed invention because the gp41 uptake moiety in the chimeric targeting protein provided additional means for gene delivery vector entering into the cells, and it is a matter of optimization and customization for the target cells of interest. Thus, the claimed invention as a whole was clearly *prima facie* obvious in the absence of evidence to the contrary.

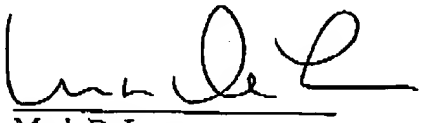
The compositions taught in *Sedlacek et al* are distinct and function differently compared to those of *Wong-Staal et al* and *Paul et al* and there would be not motivation to combine them. Neither *Wong-Staal et al* nor *Paul et al*, teaches or suggests using non-viral particles as a delivery vehicle. Rather, *Wong-Staal et al* and *Paul et al* teach the use of retroviruses that contain RNA, which upon infection is reverse transcribed into DNA that integrates in a host genome. The teachings described in *Wong-Staal et al* and *Paul et al* are directed toward the use and modification of retroviruses and are very different from the use of non-viral gene delivery systems, particularly those that include DNA. The ability to incorporate genetic material by integration into the genome of targeted cell is an important reason for using retroviruses as delivery vehicles. One skilled in the art following the teachings of *Wong-Staal et al* and *Paul et al* would not consider producing non-viral particles such as those taught by *Sedlacek et al*, and most definitely would not consider using DNA containing non-viral particles. The modifications of *Wong-Staal et al* or *Paul et al* necessary to produce the claimed invention defeat the reasons for using retroviral vectors. Such modifications would not be obvious to those skilled in the art. There would be no motivation by those skilled in the art to combine the teachings of *Sedlacek et al* with those of *Wong-Staal et al* or *Paul et al.* Those skilled in the art following the teachings of *Sedlacek et al* would not consider following the teachings of *Wong-Staal et al* or *Paul et al* which are narrowly directed at the use of retroviral vectors to deliver genes to cells.

Claims 3-6 and 37-40 are not obvious in view of the combination of *Wong-Staal et al,* and *Paul et al.* in view of *Sedlacek et al.* Applicants respectfully request that the rejection of claims 3-6 and 37-40 under 35 U.S.C. 103(a) as being unpatentable over *Wong-Staal et al*, and *Paul et al* in view of *Sedlacek et al.* be withdrawn.

Conclusion

For the foregoing reasons, Applicants respectfully request that 1, 3-6, 8, 10, 12, 13, 33, 34 and 37-42 be allowed. A notice of allowance is earnestly solicited.

Respectfully submitted,



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